Multiple-site bleeding with prominent rise in coagulation tests in an elderly woman using dabigatran etexilate

Cem Barçın, Hasan Kutsi Kabul, Emre Yalçınkaya[1], Mustafa Demir
Department of Cardiology, Gülhane Military Medical Faculty; Ankara-*Turkey*
[1]Department of Cardiology, Aksaz Military Hospital; Muğla-*Turkey*

Introduction

Dabigatran etexilate is a novel oral anticoagulant, which inhibits thrombin directly and offers an alternative to warfarin in atrial fibrillation (AF) (1-4). Dabigatran does not require routine blood testing or dose adjustments. However, increasing number of case reports show that dabigatran may change prothrombin time (PT) or activated partial thromboplastin time (aPTT) with clinical bleeding (5, 6). We, herein, report an elderly female who presented with multiple site bleeding and a dramatic increase in PT shortly after starting dabigatran.

Case Report

An 83-year-old woman (63 kg) who had been followed up for coronary artery disease and hypertension was hospitalized for pulmonary embolism and AF. After acute management in the coronary care unit we started warfarin and did not give aspirin upon the preference of the patient. During the follow up, she remained in AF. The PT was usually in target but she experienced asymptomatic increases in INR between 3.5 and 5 for a couple of times. After 9 months, she was hospitalized for bruising on the arm with PT (HemosIL™ RecombiPlasTin2G) of 86 seconds and INR of 7.8. She was on warfarin 12.5 mg per week. Her creatinine was 0.95 mg/dL (with an estimated creatinine clearance (CrCl) of 44.6 mL/min), hemoglobin was 13.8 g/dL, and liver function tests were in normal range. We stopped warfarin and started Dabigatran Etexilate 110 mg b.i.d. after the INR reduced to 1.49. After 10 days, the patient presented with severe subconjunctival hemorrhage, hematuria and hematoma in the right ankle. It had been nearly 24 hours after the last dabigatran dose and her INR was 14.8, PT was 163 seconds and aPTT was 71 seconds (Dade Actin Activated cephaloplastin reagent). Serum creatinine was 0.89 mg/dL (CrCl 47.6 mL/min) and liver tests were in normal range with the hemoglobin level of 12.4 g/dL. She was also using trimetazidine hydrochloride 35 mg b.i.d., metoprolol succinate 50 mg b.i.d., lercanidipine hydrochloride 10 mg q.d. and pantoprazol 40 mg q.d. We gave 3 units fresh frozen plasma in addition to 10 mg intravenous vitamin K. We ruled out lupus anticoagulants via mixing test. During follow up, INR reduced to 2.38 and aPTT reduced to 41 seconds. The Naranjo probability scale revealed a "probable" causality between the dabigatran and bleeding side effects. We discharged her with only aspirin of 300 mg/day.

Discussion

The present case shows that use of dabigatran etexilate may be associated with very high levels of coagulation tests even in relatively small doses in elderly patients with moderate renal impairment. Especially in case of hemorrhagic complications or in patients with high bleeding risk, it may be necessary to quantify the anticoagulant effects of dabigatran (7, 8). Dager et al. (9) showed that for every 25 ng/mL of dabigatran, INR increased 0.03 to 0.07 depending up the reagent and aPTT increased 4.6 seconds in average. In a similar study, Lindahl et al. (5) showed that 1000 ng/mL of serum dabigatran concentration resulted in INR between 1.4-4.5, and aPTT between 90-140 seconds with different reagents. In a recent case report, an increased INR level was found in a 79 year-old woman with CrCl of 20.7 mL/min/1.73 m^2 (6). Harper et al. (10) observed 44 bleeding complications among 7000 patients. Two thirds of these patients were over 80 years old, more than 50% of these elderly patients had moderate renal impairment and nearly half of them weighed less than 60 kg. Our case had similarities to this patient profile with her age and renal function but the weight was not low and the main distinction was dramatically high level of PT, which was not the case in the study of Harper et al. (10).

Conclusion

Dabigatran etexilate must be used with caution especially in elderly patients. These patients should be followed up closely even if they do not have severely impaired renal impairment and low body weight. We also speculate that exaggerated levels of PT and aPTT may be "warning sign" in high-risk patients where other more specific coagulation tests for dabigatran are not available.

References

1. Hankey GJ, Eikelboom JW. Dabigatran etexilate: A new oral thrombin inhibitor. Circulation 2011; 123: 1436-50. [CrossRef]
2. Stangier J, Clemens A. Pharmacology, pharmacokinetics, and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor. Clin Appl Thromb Hemost 2009; 15(suppl 1): S9-16. [CrossRef]
3. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. RE-LY Steering Committee and Investigators. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2009; 361: 1139-51. [CrossRef]
4. Wann LS, Curtis AB, Ellenbogen KA, Estes NA 3rd, Ezekowitz MD, Jackman WM, et al. 2011ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran): A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2011; 57: 1330-7. [CrossRef]
5. Lindahl TL, Baghaei F, Blixter IF, Gustafsson KM, Stigendal L, Sten-Linder M, et al; Expert Group on Coagulation of the External Quality Assurance in Laboratory Medicine in Sweden. Effects of the oral, direct thrombin inhibitor dabigatran on five common coagulation assays. Thromb Haemost 2011; 105: 371-8. [CrossRef]
6. Béné J, Saïd W, Rannou M, Deheul S, Coupe P, Gautier S. Rectal bleeding and hemostatic disorders induced by dabigatran etexilate in 2 elderly patients. Ann Pharmacother 2012; 46: e14. [CrossRef]
7. Gulseth MP, Wittkowsky AK, Fanikos J, Spinler SA, Dager WE, Nutescu EA. Dabigatran etexilate in clinical practice: confronting challenges to improve safety and effectiveness. Pharmacotherapy 2011; 31: 1232-49. [CrossRef]
8. Miyares MA, Davis K. Newer oral anticoagulants: a review of laboratory monitoring options and reversal agents in the hemorrhagic patient. Am J Health Syst Pharm 2012; 69: 1473-84. [CrossRef]
9. Dager WE, Gosselin RC, Kitchen S, Dwyre D. Dabigatran effects on the international normalized ratio, activated partial thromboplastin time, thrombin time, and fibrinogen: a multicenter, in vitro study. Ann Pharmacother 2012; 46: 1627-36. [CrossRef]
10. Harper P, Young L, Merriman E. Bleeding risk with dabigatran in the frail elderly. N Engl J Med 2012; 366: 864-6. [CrossRef]

Address for Correspondence: Dr. Emre Yalçınkaya,
Aksaz Asker Hastanesi, Kardiyoloji Bölümü, Marmaris, Muğla-*Türkiye*
Phone: +90 533 657 71 91
Fax: +90 312 304 42 50
E-mail: dremreyalcinkaya@gmail.com
Available Online Date: 09.06.2014

DOI:10.5152/akd.2014.5274